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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Eric OLSON *et al.*

Serial No.: 09/061,417

Filed: April 16, 1998

For: METHODS AND COMPOSITIONS FOR THERAPEUTIC INTERVENTION IN CARDIAC HYPERTROPHY

Group Art Unit: 1642

Examiner D. Minh Tam

Atty. Dkt. No.: MYOG:029US/SLH

CERTIFICATE OF MAILING
37 C.F.R. § 1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on the date below:

July 24, 2002
Date

Steven L. Highlander

DECLARATION OF RICK GORCZYNSKI UNDER 37 C.F.R. §1.132

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Rick Gorczynski, do declare the following:

1. I am currently hold the position of Vice President, Research & Development at Myogen, Inc., licensee of the above-captioned application. My education and training includes an undergraduate degree in Biological Sciences from Cornell University and a Ph.D. in Cardiovascular Physiology from the University of Virginia, School of Medicine. I have worked since 1976 in the pharmaceutical industry, primarily in the cardiovascular drug discovery field. During my 25 years in the industry I have conducted and/or supervised

research directed at a variety of cardiovascular diseases including heart failure (acute and chronic), myocardial infarction, cardiac dysrhythmia, hypertension, renal disease, hyperlipidemias and thrombosis disorders. For the past 4 years I have been exclusively engaged in the discovery and validation of molecular drug targets for use in drug discovery in the filed of heart failure. I am intimately familiar with the use of transgenic mice in the field of cardiac research and heart failure. A copy of my *curriculum vitae* is attached.

2. I am also familiar with the level of skill of scientists working in the field of cardiology and molecular biology as of the priority date of the referenced application. I consider one of ordinary skill in the art in this field of study to have a Ph.D. in biochemistry, chemistry, molecular biology, pathology or other related field, or an M.D., with 1-3 years of post-graduate study.

3. I have reviewed the specification and pending claims 1, 4, and 9 for the above-referenced case. The specification refers to the use of transfected cells and transgenic mice where NF-AT3 is either overexpressed (transfected cells) or continuously activated (transgenics) as a model for hypertrophy studies that are then held out as subsequently relevant for human studies. More specifically the specification refers to NF-AT3 transgenes lacking one or more phosphorylation sites present in wild-type NF-AT3, NF-AT3 transgenes lacking all the phosphorylation sites of the wild-type protein, and NF-AT3 transgenes lacking amino acids 1-137 of the wild-type NF-AT3 protein.

4. The inventors' paradigm, as defined through the transgenic models, was that activated calcineurin would directly bind to and dephosphorylate cytoplasmic NF-AT3. The

dephosphorylated NF-AT3 would then translocate into the nucleus where it would act as a transcription factor along with GATA-4, leading to induction of hypertrophic genes. It has not yet been shown, as the examiner correctly points out, that NF-AT3 is constitutively active or in a more active state in the hearts of hypertrophic patients. Nonetheless, NF-AT3 presents itself as an attractive candidate for therapy in cardiac hypertrophy. To that end, the inventors have targeted NF-AT3 both directly and indirectly to inhibit the onset of the transcription of hypertrophic genes.

5. I have reviewed the enclosed article by Ritter *et al.*, entitled "Calcineurin in Human Heart Hypertrophy," *Circulation*, 105:2265-2269 (2002) which supports the inventors' claims relating to NF-AT3 as a therapeutic target. The Ritter *et al.* authors set out to validate the observations made in transgenic mouse models by studying enzymatic activity and protein expression in cardiac tissue from human patients suffering from hypertrophic obstructive cardiomyopathy. While the article focuses more on the data regarding calcineurin levels in the hypertrophic hearts, the researchers also studied NF-AT2 phosphorlyation levels in normal and hypertrophic heart tissue.

Ritter *et al.* showed that, in naturally hypertrophic tissues, NF-AT2 migrated at a higher rate on a 6% SDS gel, "compared with normal heart and identical to the NF-AT migration velocity of normal heart extracts treated with additional external calcineurin" (p. 2267), providing *in vivo* evidence from a human clinical setting of an altered NF-AT phosphorlyation state in hypertrophied myocardium. This shows that NF-AT2, is in a more active, dephosphorylated form in the human hypertrophic heart, and also strongly implicates a similar finding for NF-AT3. Moreover, it validates the present inventors' notion of targeting NF-AT3 therapeutically to combat hypertrophy by interfering with the

NF-AT3 transcriptional cascade, whether by direct blocking (as in binding a molecule to NF-AT3) or by indirect effects (targeting the purported NF-AT3/GATA-4 complex).

6. With regard to the issue of using transfected cells to elucidate the interaction between NF-AT3 and GATA4, I have reviewed the attached scientific publications entitled "The Zinc Finger-containing Transcription Factors GATA-4, -5, and –6" (*J. Biol. Chem.* 275:50, 38949-38952, 2000), and "Remodeling muscles with calcineurin," (*BioEssays* 22:510-519, 2000). Based on the results set forth in these papers, it is clear to me that a person of ordinary skill (as defined above) would recognize that the art currently accepts that NF-AT3 does indeed interact with GATA-4, although the has not been shown directly. Perhaps the best information on this point comes from the latter paper, a mini-review of the state of the art, published over a year and a half ago. This article states that "GATA-4 also physically interacts by way of the C-terminal zinc finger with nuclear factor of activated T-cells-c4 (NFAT)" (p. 38951; also see Molkentin, *Cell* 93, 215; and Morin, *EMBO J.*, 19, 2046).

In conclusion, though no single experiment demonstrates a physical interaction between GATA-4 and NF-AT3, the aforementioned authors, as well as those of ordinary skill in the art in the field of cardiac biology, believe that such an interaction takes place. Further, it is my opinion that targeting this interaction using the approaches set forth in the present specification, with which is am quite familiar, is a valid approach to the treatment of hypertrophy. In particular, the use of GATA-4 mimetics and other small molecules that would interrupt the NF-AT3/GATA-4 interaction would be expected to interfere with NF-AT3's stimulation of the hypertrophic genes, providing a benefit to the patient.

7. I hereby declare that all statements made of my own knowledge are true and all statements made on information are believed to be true and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

July 3, 2007
Date

Richard Gorczynski
Rick Gorczynski, Ph.D.